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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HORNING, MICHELLE S	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,980	IIAN ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191 AND 205* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-26,129-151,154-177,183-185,187,189-191,197,198,200-202 and 205.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-5,7-10,12-42,46,53,55-58,61-74,77-96,98-108,110-118,121-123,129-150,154-160,171-177,183,185,187,189,197,198 and 200-202.

DETAILED ACTION

This action is responsive to communication filed 9/19/2008. Any objection or rejection not reiterated herein has been withdrawn.

Claim Rejections - 35 USC § 112-MAINTAINED

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modulation of an immune response related to hepatitis and colitis, does not reasonably provide enablement for treatment of any kind disease associated with inflammatory responses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Enablement is considered in view of the *Wands* factors.

Nature of the invention. The invention is drawn to a method for the treatment of a disease wherein there is an inflammatory immune response comprising administering a mammalian intermediary metabolite to a mammal.

State of the prior art. The prior art teaches the differences in ligand specificity between NKT cells, using multiple ceramides including glucocerebroside or glucosylceramide (see Makowska et al, whole document). Makowska et al teach that

αGalCer and other glycolipid variants stimulate V α14+ NKT cells (see Discussion). Also, see page 72 which lists the various ceramides.

Breadth of the claims. The claims are broad, encompassing the treatment of any and all diseases in which an inflammatory response is associated. Applicants have suggested throughout the REMARKS that limiting the claims to a disease associated with an inflammatory response "limits the particular diseases that would be used with the current invention *since many diseases do not involve an inflammatory response* and for most diseases that do involve an inflammatory response, this response is part of the curative process rather than the pathogenesis" (emphasis added). This recitation is noted for reasons of record. ***Applicant is invited to provide references which teach that many diseases do not involve an inflammatory response.***

Working examples. The working examples are specifically directed towards glucocerebroside treatment of a Con A-induced hepatitis model, a colitis model and a model for non-alcoholic steatohepatitis. The working examples provide no parallel towards the successful treatment of inflammatory responses for all possible diseases. Applicants state that the differential diseases "share the common feature of an inflammatory process responsible for the symptoms of the disease". The recitation is noted for reasons of record. In response, the Examiner invites the Applicants to provide further elucidation and point out the support in the instant specification. What common feature? Also, please note that paragraph 48 provides the following recitation: "The treatment of a disease may also result in a change the cytokine responses. Any cytokine in the immune system may be involved in these responses. The change could

result in a pro-inflammatory or an anti-inflammatory response. There may also be a pro-inflammatory, and an anti-inflammatory response since certain cytokines may increase and others may decrease, simultaneously." This recitation is emphasized merely to show that the inflammatory response is complex and can be very different depending on disease. Thus, the cytokine production is not a common ground.

Guidance in the specification. The specification provides little guidance regarding the practice of the methods as claimed. It is not clear what the Applicant is arguing. Applicants state that it is not a requirement for the practice of the invention that all parameters be known for all diseases. In response, something must be known to claim the treatment of all diseases with an inflammatory response and the specification lacks disclosing it.

Predictability of the art. There is none. Diseases lead to differential responses and there can be no predictability in treating them all; see discussion above with respect to differential productions of cytokine provided by the instant specification. The argument is not clear. Applicant provides the following: "many diseases do not involve an inflammatory response at all" and diseases with an inflammatory response is "describing a limited group of diseases" and the specification is drawn to "the common factor that is being treated". Of note, the common factor must not be the differential cytokine response as the instant specification describes in paragraph 48.

Amount of experimentation necessary. It would require years of further research to develop effective therapy for any and all diseases with an inflammatory response. Applicant recites the following: "Applicants respond that it is quite *unrealistic* to state

that it would take years to practice the present invention when three separate working examples have actually been disclosed. Furthermore, as described above, Applicants have included limitations in Claim 1 thereby showing that the diseases are restricted to ones that have pathology contributed by immune reactivity and that the mammalian intermediary metabolites used for treatment of the disease are limited to lipids and glycolipids. These limitations are part of the exemplifications of the three disease models described above and as such, create a closer association between the claimed method and the disclosed examples.

In conclusion, Applicants believe that the disclosures provided in the specification of the present invention not only do not necessitate undue experimentation, but also severely limit the requirement of any additional experimentation to carry out the claimed invention".

In response, it would be "quite unrealistic" to claim a method of treating any and all diseases associated with an inflammatory response. Diseases associated with such a response would include cancer, heart disease, Pelvic Inflammatory Disease, Bowel Disease, many periodontal diseases, allergies and asthma and much more. The specification does not disclose any common feature among any disease that was successfully treated. The three working examples do not demonstrate that their successful treatment would also lead to the successful treatment of all diseases with an inflammatory response. The phrase, diseases with an inflammatory response, fails to describe a limited group of diseases. Further, it is absolutely untrue that many diseases do not involve an inflammatory response. Not one argument is found to be persuasive.

Thus, it would take years to develop a method as claimed *if even possible at all*. No argument is found to be persuasive.

Response to Arguments

Applicant's arguments filed 9/19/2008 have been fully considered but they are not persuasive. Applicant asserts that the claims are not drawn to any kind of disease associated with inflammatory responses but to those in which the inflammation contributes to the pathogenesis of said disease. While true, there is little distinction between the two as the claim does not require any specific amount of contribution of the inflammation to the pathogenesis. Since various diseases associated with inflammatory responses would be expected to have some contribution somewhat related to the pathogenesis, there is no clear distinction set forth by said contribution. Applicant also argues that most diseases involved in inflammatory response are part of the curative process rather than the pathogenesis. This too is a hard line to distinguish as even a curative process in the body may relate to a pathogenesis (e.g. autoimmune diseases). Further, even diseases which have a curative inflammatory response may also have the same immune response as part of the manifestation of the disease to at least some level (e.g. complications etc). While Applicant is correct with respect to the notion that not all disease invoke inflammatory diseases, the number of diseases that do are so vast, of diverse etiology and unrelated in their origin and methods of treatment. Thus, the number of diseases that do invoke inflammatory response is extremely diverse as well as not completely recognized. Applicant asserts that the very specific examples of treatment in the specification provide a parallel to inflammatory responses to all

diseases. This would not be expected as the number of diseases related to inflammation even with contribution to pathogenesis is so large that these specific examples do not show that they are indeed parallel. For example, such diseases would include cancer, heart disease, bacterial disease, viral infections etc. and no single drug is recognized in the prior art to treat such a diverse set of conditions. For example, the role of inflammation for various diseases may or may not be recognized at this point. However, it is known to be a factor in an extremely diverse set of diseases and a drug that may be effective for treating one disease associated with inflammation will not be necessarily useful for treating another. For instance, an anti-inflammatory such as aspirin would not be expected to be recognized as a chemotherapeutic drug. However, cancer is associated with inflammation.

Claim Rejections - 35 USC § 102-MAINTAINED

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75, 97, 109, 119-120, 124-126, 151, 157, 161-168 and 184 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6610835 (hereinafter as "Liotta").

Liotta et al describe the use of sphingolipid derivatives and their methods of use, including in the treatment of inflammatory conditions (see Abstract and Figures for chemical structures including ceramide, lactosylceramide and mammalian sphingomyelin). Paragraph 17 (Background of the Invention) describes how mice were fed diets with sphingomyelin supplemented foods. The authors disclose that such a compound is suited for the treatment of colitis (see paragraph 39, Summary of the Invention). Paragraph 541 provides sphingolipid conjugates. Paragraphs 641 provide terminally polar sphingolipids. Paragraph 543 describes antigens derived from immunized animals. Liotta et al teach using synthetic analogs of sphingosine throughout the entire document. Conjugates can be or include an enzyme for converting a prodrug into a drug (see Paragraph 555). The authors provide the same method steps comprising administering the same ingredient to the same population. Inherently, this would result in the same effects, including changes in cytokine responses, NKT cells or Th1/Th2 balance.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical

processes, a prima facie case of either **anticipation** or obviousness has been established.

In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

Thus, the claims above are rejected.

Response to Arguments

Applicant's arguments filed 9/19/2008 have been fully considered but they are not persuasive. Note that this rejection has been changed to a 102(e) due to an inadvertent error but the merits of the rejection remain the same. Applicant asserts that Liotta teaches that natural forms of sphingolipids are inadequate and only teaches the use of sphingolipid derivatives. The relevance of this argument is unclear. No such exclusion of sphingolipid derivatives is claimed. The claims only require (e.g. claim 1) that the intermediate metabolite "comprises" a lipid or a glycolipid and clearly the sphingolipid derivatives of Liotta comprise a lipid. It is noted that the claims do not recite a metabolite of a lipid but that said metabolite only "comprises" a lipid or glycolipid. For example, the disclosure in Liotta of lactosylceramide is clearly within the scope of the claims.

Claim Rejections - 35 USC § 103-MAINTAINED

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al, Makowska et al (2000) and Tanguchi et al (cited in the IDS).

The teachings of Liotta et al is applied as discussed above. Liotta et al does not explicitly teach using CD1 receptor presenting cell, glucosylceramide or galactosylceramide, or food deprivation.

Liotta et al describe how sphingolipids are found in a number of foods, including wheat flour, potato and beans. It would have been obvious to the ordinary artisan to deprive the subjects of any food before providing them with the sphingolipid supplemented food specific for treatment. One would have been motivated to do so in order to control the concentration of the sphingolipids administered as well as control the effect. There would have been a reasonable expectation given this practice widely

practiced and commonly known. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Separately, Makowska et al examine the difference in the ligand specificity between CD1d-restricted T cells with limited and diverse T-cell receptor (TCR) repertoire. The author used multiple ceramides which are listed on page 72. They include alpha-glucosylceramide and beta-galactosylceramide. Table 3 provides the responsiveness of CD1-reactive hybridomas with diverse TCR to the differential ceramides presented on CD1-transfectants. Additionally, Figure 5 depicts the responsiveness of KT/23 hybridoma comprising Valpha14+. Note that the supernatants were harvested and examined for IL-2 content in a CTLL assay (see corresponding figure legend). In conclusion, the authors demonstrate that alpha-glucosylceramide in stimulating NKT cells (Valpha14+); see conclusions on page 77.

Taniguchi et al teach a treatment method in which glycosylceramides and derivatives are used as the active ingredients in activating NKT cells; this method serves as remedies for diseases and disorders, including ulcerative colitis (whole document). The structure of glucocerebroside is disclosed on page 3. Further, "antigen presenting cells treated with KRN 7000 showed a marked stimulative effect on Va24+ NKT cell proliferation in a manner dependent on the number of antigen-presenting cells" (page 18, lines 57-58, also see Figure 9 on page 36). Taniguchi et al disclose the use of autologous antigens in the following quote "an autologous mixed leukocyte reaction (MLR) was performed using these antigen-presenting cells as stimulator cells and

autologous peripheral blood mononuclear cells as responder cells" (page 18, paragraph 98).

Thus, it would have been obvious to one of ordinary skill in the art to combine the teachings above in order to perform a method of administering an intermediary metabolite in combination with antigen presenting cells. More specifically, Makowska et al provide that alpha-glucosylceramide stimulates NKT cells and Taniguchi et al provides the method of using antigen-presenting cells. One would have been motivated to combine the teaching in order to modulate the IL-2 content of a subject. There would have been a reasonable expectation of success given the alpha-glucosylceramide effects are well-characterized by Makowska et al and administering antigen-presenting cells is commonly known. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 9/19/2008 have been fully considered but they are not persuasive. Applicant avers that Liotta neither teaches nor discloses administration of mammalian intermediary metabolites. As state above, the metabolites are defined in the claim as only comprising a lipid or a glycolipid. This is clearly met by the sphingolipid derivatives as disclosed by Liotta. For example, the disclosure in Liotta of lactosylceramide is clearly within the scope of the claims. Applicant asserts that Makowska teaches away from the use of natural glucosylceramides by an observation of complete ineffectiveness of the beta form as compared to the alpha form. This argument is unclear as the claims are not limited to any specific conformation.

Applicant asserts that none of the references teaches the use of a normal mammalian intermediary metabolite but instead teaches the use of non-natural products. Again, the claims are limited only to the administration of a lipid or glycolipid as defined by the claims. This clearly met by the prior art.

Double Patenting-MAINTAINED

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim1-7 and 9-15 of copending Application No. 11/378, 941. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed towards administering the same compounds

which induce the same effects (NKT cell modulation and cytokine production). Applicant did not respond to the merits of the rejection but only provided a request that the rejection be held in abeyance.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michelle Horning/
Examiner, Art Unit 1648
/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648